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Examining Group 1625
Patent Application
Docket No. GJE-136D1
Serial No. 09/928,139

Doran R. Pace, Patent Attorney

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Celia C. Chang
Art Unit	:	1625
Appellants	:	Marianne Langston, Hooshang Shahriari Zavareh
Serial No.	:	09/928,139
Filed	:	August 10, 2001
For	:	Manufacture of Single Isomer Methylphenidate

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Alexandria, VA 22313

REQUEST FOR REINSTATEMENT OF THE APPEAL UNDER 37 CFR 1.193(b)(2)(ii)

Sir:

In response to the Office Action dated September 29, 2004, Appellants hereby request reinstatement of the appeal for which a Notice of Appeal was filed March 19, 2004. Enclosed herewith please find Appellants' Supplemental Appeal Brief Under 37 CFR §1.193 (in triplicate).

Any fees as required by 37 CFR §1.16 or §1.17 should be charged to Deposit Account No. 19-0065.

Respectfully submitted,

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DRP/sl
Attachment: Supplemental Appeal Brief Under 37 CFR §1.193

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Celia C. Chang
Art Unit	:	1625
Appellants	:	Marianne Langston, Hooshang Shahriari Zavareh
Serial No.	:	09/928,139
Filed	:	August 10, 2001
Confirm. No.	:	6929
For	:	Manufacture of Single Isomer Methylphenidate

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SUPPLEMENTAL APPEAL BRIEF

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Doran R. Pace, Patent Attorney

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I. REAL PARTY IN INTEREST

This application is owned by Celltech Pharma Europe Limited.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1-8 are pending in application Serial No. 09/928,139 (hereinafter the '139 application) and are under non-final rejection. The claims were under final rejection in the Office Action dated December 19, 2003. Appellants filed a Notice of Appeal on March 19, 2004 appealing the rejections of all claims. Appellants filed an Appeal Brief on July 19, 2004. The finality of the rejections in the December 19, 2003 Office Action was withdrawn following a Patent Office appeal conference and a non-final Office Action was mailed on September 29, 2004.

The final rejection of claim 1 for lack of enablement under 35 USC §112, first paragraph, as set forth in the final Office Action dated December 19, 2003 has not been reiterated in the September 29, 2004 non-final Office Action; therefore, Appellants have assumed that this rejection has been withdrawn and have not addressed it in this Supplemental Appeal Brief. If the Examiner intended that the rejection of claim 1 for lack of enablement under 35 USC §112, first paragraph, is maintained, then Appellants, in accordance with the provisions of MPEP 1208.02, hereby incorporate by reference and in their entirety the arguments directed to the rejection as submitted in the Appeal Brief filed July 19, 2004.

All pending claims have been twice rejected and the rejection of claims 1-8 is hereby appealed. A Request for Reinstatement of the Appeal under 37 CFR 1.193(b)(2)(ii) is submitted with this Supplemental Appeal Brief.

IV. STATUS OF AMENDMENTS

No amendments to the claims were filed subsequent to the final Office Action dated December 19, 2003 or Office Action dated September 29, 2004 which reopened prosecution of the '139 application following filing of a Notice of Appeal dated March 19, 2004 and Appellants' Appeal Brief dated July 19, 2004. The claims as currently pending are attached hereto in Appendix A.

V. SUMMARY OF THE INVENTION

The subject invention provides methods for obtaining single enantiomer *d-threo*-methylphenidate or *l-threo*-methylphenidate. Methylphenidate is a therapeutic agent used in the treatment of attention-deficit hyperactivity disorder (ADHD). Methylphenidate contains two chiral centers in the molecule and, therefore, racemic methylphenidate is made up of four separate stereoisomers: *d-threo*-methylphenidate, *l-threo*-methylphenidate, *d-erythro*-methylphenidate, and *l-erythro*-methylphenidate. Of the four stereoisomers, the *d-threo*-methylphenidate isomer is consider to have the preferred therapeutic activity. A mixture containing both the *d-threo*-methylphenidate and the *l-threo*-methylphenidate stereoisomers can be resolved into the individual *d-threo*-methylphenidate and *l-threo*-methylphenidate stereoisomers using standard resolution methods known in the art, examples of which are described in the subject specification (see page 3, lines 2-6). However, following the resolution step, it is desirable to be able to recycle the unwanted stereoisomer so as to minimize waste and provide for an economically viable process for producing the desired single stereoisomer of methylphenidate. The subject invention provides for recycling of the unwanted stereoisomer based on Appellants' discovery of means to effect racemisation of a single stereoisomer of methylphenidate at both chiral centers of the molecule so as to produce a racemic mixture of all four stereoisomers, which can then be resolved into the individual stereoisomers and the cycle continued. Thus, the subject invention provides for recycling of an unwanted methylphenidate stereoisomer to produce racemic methylphenidate, which can then be

used in the claimed method. The specification of the '139 application, at page 3, lines 12-20, describes treatment of the unwanted stereoisomer with an acid in order to effect racemization of the unwanted single stereoisomer at both chiral centers of the molecule to produce a racemic mix of all four stereoisomers. A specific embodiment for racemization of the unwanted stereoisomer using a carboxylic acid and heat is described at page 3, lines 13-15, of the subject specification. Methods for resolving enantiomers of methylphenidate using a chiral acid, such as O,O'-ditoluoyltartaric acid, are described at page 3, lines 3-4 and lines 20-21, of the subject specification.

VI. ISSUES

Four issues remain for resolution:

A. Whether the claim to foreign priority under 35 USC 35 §119 will be acknowledged in the subject '139 application.

B. Whether claims 1-8 are unpatentable under 35 USC §103(a) as obvious over any of:

1) Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261); or

2) Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

C. Whether claims 1-8 are unpatentable under the judicially created doctrine of obviousness-type double patenting over claim 1 of U.S. Patent No. 6,121,453 in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

D. Whether the Harris patent (U.S. Patent No. 6,242,464) is disqualified as prior art under 35 USC §103(c) in the rejection under 35 USC §103(a) in which the Harris patent is cited.

VII. GROUPING OF CLAIMS

Claims 1-6 and 8 are rejected under 35 USC §103(a) as obvious over Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261). Claims 1-6 and 8 do not stand or fall together under this rejection.

Claims 1-8 are rejected under 35 USC §103(a) as obvious over Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464). Claims 1-8 do not stand or fall together under this rejection.

Claims 1-8 are rejected under the judicially created doctrine of obviousness-type double patenting over claim 1 of U.S. Patent No. 6,121,453 in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464). Claims 1-8 do not stand or fall together under this rejection.

VIII. ARGUMENT

A. The '139 application is entitled to a claim of foreign priority under 35 USC §119.

In the Office Actions in the subject '139 application, the Examiner has not acknowledged Appellants' claim to foreign priority under 35 USC §119 although such claim was brought to the Examiner's attention in three separate communications to the Patent Office, two of which included a copy of Appellants' formal claim to foreign priority that was originally submitted with the filing of

the '139 application. In the Office Action dated December 19, 2003, the Examiner again did not acknowledge Appellants' claim to foreign priority, stating that the "records of filing and claiming such benefit under 35 USC 119 be made of record for [the '139] application." In the remarks section of the Office Action dated September 29, 2004, the Examiner indicated that "the priority benefit of the instant application is limited to Sept. 10, 1996 since the GB 9602174.6 application is drawn to racemization by derivatization into olifinic intermediates (not stereo isomers) instead of the instantly claimed racemization of the unwanted enantiomers." Appellants assume from the Examiner's statement in the September 29 Office Action that the Examiner is acknowledging Appellants' foreign priority claim to British application number GB 9618836.2 filed September 10, 1996. However, the Examiner did not acknowledge any foreign priority claim on the September 29 Office Action Summary sheet (PTOL-326) of the '139 application.

Moreover, Appellants respectfully assert that foreign priority application GB 9602174.6 does disclose Appellants' claimed invention and, therefore, the subject '139 application is entitled to the earlier foreign priority date of February 2, 1996. At Page 1, first full paragraph in the "Description of the Invention" section of the GB 9602174.6 application, it is stated that "This invention is based on the novel discovery of methods to effect epimerization of *both* chiral centres in methylphenidate." At page 2 of the GB 9602174.6 application, second full paragraph, it is stated that

> The invention is the racemization which requires epimerization at both stereogenic centres. We have discovered that such racemization can be carried out by way of activation at the piperidine nitrogen to promote fragmentation of the ring. The resultant olefinic intermediate has no chirality and recloses to [form] a racemic mixture." (emphasis added)

Thus, the process does not end at the olefinic intermediate, as suggested by the Examiner, but continues through to form a racemic mixture of stereoisomers. Scheme 2 on page 2 of the GB 9602174.6 application also shows racemization starting with an "unwanted enantiomer" of methylphenidate with the resultant product being a racemate. Means to effect the racemization are disclosed in the last paragraph on page 2 through to the end of page 3 of the GB 9602174.6 application. Thus, contrary to the Examiner's assertion, the GB 9602174.6 application does disclose racemization of an unwanted enantiomer through to a racemic mixture of enantiomers.

Accordingly, acknowledgement of Appellants' claim to foreign priority for both the GB 9602174.6 and GB 9618836.2 British applications under 35 USC §119 in the subject '139 application is respectfully requested.

B. Claims 1-8 are not *prima facie* obvious over any combination of:

i) Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261); or

ii) Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

1. Statement of the rejections under 35 USC §103(a).

Claims 1-6 and 8 are unpatentable under 35 USC §103(a) as obvious over Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261); and claims 1-8 are unpatentable under 35 USC §103(a) as obvious over Zeitlin *et al.* (U.S. Patent No. 5,733,756) or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

The basis for the rejections over the combination of Zeitlin *et al.* or Armstrong *et al.* (1986) in view of Barry (1993), Miller (abstract 1980), or Miller (U.S. Patent No. 4,254,261), as set forth in the Office Action dated September 29, 2004, is quoted below:

> *Determination of the scope and content of the prior art (MPEP §2141.01)*
>
> Zeitline '756 or Armstrong et al. disclosed processes for making a single enantiomer of d-threo-methylphenidate or l-threo-methylphenidate from racemic mixtures. See Zeitline '756 col. 6-7, example 5, and col. 6, example 4 wherein both acid or ester can be used to obtain the single isomer. See Armstrong's whole article with methylphenidate exemplified on page 1133 last compound of table 1.
>
> *Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)*
>
> Zeitline or Armstrong disclosed all the elements of the claims **except** wherein a recycle by racemization step was not included. Barry taught that in preparation of amino acid esters (please note that the instant methylphenidate is a cyclic amino acid

ester) analogous to the claims, racemization is achieved under acidic conditions and the analogous art by Miller (CA 94) or '261 taught that recycling the racemized isomers would give more of the intended isomer (see Miller's abstract and '261 col. 1 lines 64-66). In addition, both heat and acid were taught by the prior art as agents for racemization (see Barry and Miller).

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

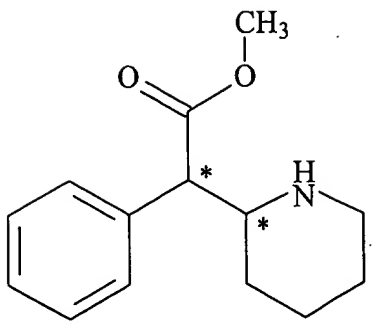
One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references placed the single enantiomer, process of making and alternative choices for increasing yield of a single isomeric form in the possession of an artisan in the field. It would have been prima facie obvious to employ a conventional modification of recycle/racemization step for the conventional process of Zeitline or Armstrong **because** producing higher yields of a desirable single isomer is expected, and such expectation is the attributes taught by the prior art. The teaching of Zeitline that either a free acid or ester can be separated suggested to one skilled in the art that a racemization step can be either before or after esterification.

Based on the combination of references cited, the Examiner concludes that the invention set forth in claims 1-8 would have been obvious to a person of ordinary skill in the art.

2. A *prima facie* case of obviousness has not been established against claims 1-8.

Appellants respectfully assert that the claimed invention is not obvious over the cited references, regardless of whether the references are taken alone or in combination. In order to establish a *prima facie* case of obviousness, the prior art must teach or suggest each and every element and limitation of the claimed invention, and provide a reasonable expectation of success that the modification or combination will succeed. *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988). A *prima facie* case of obviousness has not been established against claims 1-8 in the subject '139 application because none of the cited references, taken alone or in the combination asserted by the Examiner, teach or suggest each and every element of Appellants' claimed invention, nor do the cited references provide the required reasonable expectation of success.

The claimed invention of the subject '139 application relies on racemization of a single enantiomer of methylphenidate. The product of such racemization is all four possible enantiomers of methylphenidate. Methylphenidate has the following structure, wherein each * represents a chiral center within the molecular structure:



As can be understood from the above structure, methylphenidate has two chiral centers within the molecule.

The Zeitlin *et al.* patent (U.S. Patent No. 5,733,756) and the Armstrong *et al.* (1986) reference are cited by the Examiner as teaching methods for preparing single enantiomer *d-threo*-methylphenidate or *l-threo*-methylphenidate from racemic mixtures of methylphenidate. Appellants acknowledge that the primary references relied upon by the Examiner, Zeitlin *et al.* or Armstrong *et al.*, disclose single enantiomer methylphenidate; however, neither the Zeitlin *et al.* or Armstrong *et al.* references teach or suggest methods for racemizing methylphenidate (or any other single molecule with two chiral centers) at both of the chiral centers in the molecule, *i.e.*, wherein every one of the four possible stereoisomers of methylphenidate is produced. The Examiner acknowledged in the Office Action dated September 29, 2004 that the Zeitlin *et al.* and Armstrong *et al.* references do not teach a racemization step. Appellants respectfully assert that none of the other references cited in the rejections under 35 USC §103 teach or suggest methods for racemizing methylphenidate at both of the chiral centers in the molecule. Appellants' discovery and utilization of a means for racemizing methylphenidate at both chiral centers of a single enantiomer is a critical aspect of the invention that the Examiner has yet to fully appreciate or take into consideration when applying the references cited under the rejections.

A key aspect of the invention lies with the difficulty in producing a racemic mixture comprising all four stereoisomers of methylphenidate when starting with but a single stereoisomer of methylphenidate. Prior to Appellants' invention, there was no teaching or suggestion in the art of being able to racemize methylphenidate at both of the chiral centers of the molecule. This is

evidenced by the lack of a reference being cited by the Patent Office specifically teaching the racemization of a single enantiomer of methylphenidate so as to produce all four possible stereoisomers, even after several years of prosecution of the subject application and the parent application. In making the rejections under 35 USC §103, no evidence or references have been presented or cited by the Patent Office which teach or suggest, with the required reasonable expectation of success, how an ordinarily skilled artisan might effect racemization of a single enantiomer of methylphenidate at both chiral centers of the molecule. Appellants note that the teaching or suggestion and the reasonable expectation of success must be founded in the prior art; Appellants' disclosure cannot be used for hindsight reconstruction of the prior art for a rejection under 35 USC §103. *In re Sponnoble*, 160 USPQ 237 (CCPA 1969). The fact that at the time of the subject invention methylphenidate was known in the art and that methylphenidate was known to have two chiral centers does not put the ordinarily skilled artisan in possession of a means for racemizing a single stereoisomer of methylphenidate to produce all four stereoisomers of methylphenidate, in the absence of a teaching in the art of a means to effect such a racemization with a reasonable expectation of success. The Examiner has not indicated where in any of the cited references one can find a teaching or suggestion of a means for racemizing a single enantiomer of methylphenidate (or even an enantiomer of some other molecule having a chemical structure similar to methylphenidate and having two chiral centers) that would have predictably produced all four possible stereoisomers of methylphenidate. Appellants respectfully submit that the Examiner has not indicated where in the cited references one can find the requisite teaching or suggestion because none of the cited references disclose a means for racemizing a single enantiomer of methylphenidate, or at least a molecule that has two chiral centers and that is structurally analogous to methylphenidate, into all four possible stereoisomers.

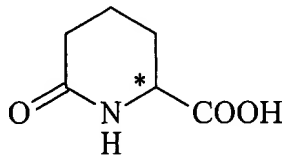
The secondary references cited by the Examiner in the Office Actions in the subject '139 application do not overcome the deficiencies of the primary references. Under both of the obviousness rejections, the Examiner asserts that "it is well known in the art that when compounds possess two chiral centers four enantiomers exist as its innate nature,..." Appellants do not deny that if one knows that a molecule has two chiral centers, then one also knows that four distinct stereoisomers of the compound can exist. However, knowing a thing **can exist** and actually

producing the thing so that it **does exist** are two completely separate matters. Just because one knows a thing can exist does not mean one has the capability to make the thing. This is at the heart of many inventions: discovering how to produce something that had never been produced before even if one knew that the something could exist or did exist in nature. The Examiner asserts that the Barry reference teaches "that in preparation of amino acid esters (please note that the instant methylphenidate is a cyclic amino acid ester) analogous to the claims, racemization is achieved under acidic conditions" and that the Miller references (characterized by the Examiner as "analogous art") teach "recycling the racemized isomers would give more of the intended isomer." The Harris patent is cited as teaching that the limitation of claim 7 is conventional "since the same compound and the same reagent have been used in purifying the enantiomer as claimed...."

In regard to the Barry reference, Appellants respectfully assert that the amino acid esters (*e.g.*, leucine methyl ester) disclosed in the Barry reference have only **one chiral center** within the molecule itself. Thus, any racemization that may be taught in the Barry reference is racemization of a molecule with a single chiral center, and not racemization of a single molecule with two chiral centers as provided in Appellants' claimed invention. Therefore, the amino acid esters taught in the Barry reference are **not structurally analogous** to methylphenidate and the racemization of such amino acid esters is not analogous to the racemization of methylphenidate. The Examiner's comments regarding the "obviousness" to employ methods for racemization as taught by the Barry reference may be relevant where the compound to be racemized has only one chiral center, but are not relevant where the compound to be racemized has two chiral centers. An ordinarily skilled artisan would expect that racemizing a molecule having two chiral centers would require at least two steps, and the nature of the steps would likely be entirely distinct. However, the Examiner has not addressed or acknowledged the distinction of a molecule with one chiral center compared to a molecule with two chiral centers. Accordingly, Appellants respectfully assert that the Barry reference does not teach or suggest an individual molecule that has two chiral centers formed by the structural arrangement of the atoms of the molecule and, moreover, does not teach or suggest anything concerning a means for racemizing a molecule, such as methylphenidate, having two chiral centers so as to produce all four possible stereoisomers from a single enantiomer of the molecule.

Appellants' respectfully disagree with the Examiner's position that the compounds disclosed in the Barry reference are "analogous" to that of Appellants' claimed invention and again stress that **methylphenidate has two chiral centers whereas the amino acid esters disclosed in the Barry reference have only one chiral center.** The Examiner has not explained how a molecule with one chiral center can be considered "analogous" to a compound having two chiral centers, nor has the Examiner provided any evidence or reasoning to support the Examiner's position that the amino acid esters disclosed in the Barry reference are analogous to methylphenidate. Moreover, the Examiner has failed to address Appellants' arguments and evidence (in the form of the Prashad reference and the Declaration by Dr. Zavareh submitted previously and discussed herein). If the Examiner maintains that the amino acid esters of the Barry reference are structurally analogous to methylphenidate, then Appellants respectfully assert that the Examiner explain in detail in the Examiner's Answer how an amino acid ester molecule having only one chiral center is structurally similar to a molecule of methylphenidate having two chiral centers.

Appellants also respectfully assert that the compound that is described in the Miller references (abstract (1980) and U.S. Patent No. 4,254,261), homopyrrolidone carboxylic acid (hereinafter referred to as HPCA), has only one chiral center. Thus, Appellants respectfully assert that the Miller references, contrary to the Examiner's assertion, are not analogous art. The HPCA compound, whose resolution is disclosed in the Miller references, is represented by the following formula, wherein the * represents a chiral center:



Appellants stress that the above compound, like the amino acid esters described in the Barry reference, has only **one chiral center** within the molecule itself. The '261 Miller patent specifically states, at column 1, lines 58-60, that HPCA exists as "the S-enantiomer, the R-enantiomer, and the R,S-racemate." Thus, it is clear from the disclosure in the Miller references that HPCA has one chiral center and, therefore, can exist only as two (not four) enantiomers: R-HPCA and S-HPCA. Dehydroabietylamine (DAA) is a chiral molecule, which is disclosed in the '261 Miller patent as

forming a salt with HPCA; however, racemization of DAA is not described in the cited Miller references. Only a racemic mixture of R-HPCA and S-HPCA as free acid, or the mixture of the salts R-HPCA.DAA and S-HPCA.DAA, is described in the cited Miller references. Although a mixture of the salts R-HPCA.DAA and S-HPCA.DAA is formed, the enantiomeric salts (different enantiomers of HPCA; same enantiomer of DAA) are separated. Otherwise, there would be no effective resolution. Moreover, the formation of a salt between HPCA and DAA is not equivalent to a single molecule having two chiral centers, wherein an enantiomer of the single molecule can be racemized to form four separate, distinct stereoisomers.

As noted above, it is only HPCA that is disclosed in enantiomeric forms and HPCA only has a single chiral center. The Miller abstract merely discloses racemizing an enantiomer of HPCA. Specifically, the Miller abstract discloses racemizing either enantiomer of HPCA (referred to therein as the "D" and "L" enantiomers) by heating the enantiomer at 205-250 degrees for a few minutes, followed by resolution of the racemate into D-HPCA and L-HPCA, wherein the L-HPCA was then racemized for recycling into a resolution step. There is no teaching or suggestion in the Miller abstract of racemizing an enantiomer of a molecule that has two chiral centers. In addition, the Miller abstract does not teach or suggest racemization by reacting an unwanted enantiomer with an acid, as is recited in Appellants' claims. Thus, the Miller references do not teach or suggest an individual molecule that has two chiral centers formed by the structural arrangement of the atoms of the molecule, nor do the Miller references teach or suggest means for racemizing a single enantiomer of a molecule with two chiral centers to give all four different stereoisomers. It is only the disclosure in the '139 application that teaches racemization of an enantiomer of methylphenidate into all four stereoisomers.

In addition, the Examiner has not provided any scientific basis to support the assertion in the Office Action dated September 29, 2004 that one would only have to employ a "conventional modification of recycle/racemization step for the conventional process of Zeitline or Armstrong" to render Appellants' claimed process obvious. The Examiner failed to state in the Office Action what that "conventional modification" is, or why it would be considered "conventional." In establishing a *prima facie* case of obviousness, the burden is on the Patent Office to provide an evidentiary basis for asserting logic and scientific principles in support of the rejection. *In re Grose*, 201 USPQ 57

(CCPA 1979) ("When the PTO seeks to rely upon a chemical theory, in establishing a prima facie case of obviousness, [the PTO] must provide evidentiary support for the existence and meaning of that theory."). In the '139 application, no evidentiary basis has been provided and, therefore, a *prima facie* case of obviousness has not been established.

The Examiner cites several references to supplement the rejection. First among these, the Branko *et al.* reference (actually, the correct citation of the reference is Jursic *et al.* as Branko is the first name and Jursic is the last name of the first author but Appellants will use the Branko *et al.* name used by the Examiner to avoid confusion on the record), is cited by the Examiner as teaching "when compounds possess two chiral centers four enantiomers exist as its innate nature . . .." The Examiner also cites the Branko *et al.* reference as showing that all four enantiomers of methylphenidate existed in mixture until separation. Appellants acknowledge that if a compound is known to have two chiral centers, then four possible enantiomers of the compound can exist. However, while the Branko *et al.* reference may teach a mixture of all four enantiomers of methylphenidate and teach agents for resolving enantiomers, the reference does not teach how to prepare the mixture of all four enantiomers when starting from a single enantiomer of methylphenidate.

The next supplementary reference, Frigerio *et al.*, is cited by the Examiner as "evidence supporting the innate nature of the four enantiomers mixture . . .." The Examiner asserts that the results in Frigerio *et al.* are surprising because, according to the Examiner, synthesis of the reboxetine compound described in the reference resulted in only two enantiomers rather than the four enantiomers expected. Appellants note that the Frigerio *et al.* reference cited by the Examiner and provided with the Office Action was an abstract of an article. Appellants have obtained the complete, full-text Frigerio *et al.* reference, and a copy of that reference is attached as Appendix B of this Appeal Brief. In the full-text Frigerio *et al.* reference, it is clear that in regard to the synthesis of two rather than four enantiomers of reboxetine, the synthesis was stereo-specific (see page 351, column 2, lines 14-18, of the Frigerio *et al.* reference and see reference 4 (Melloni *et al.*) cited therein), meaning that it was intended that only two of the four enantiomers were synthesized (and, therefore, was not surprising). Moreover, the Frigerio *et al.* reference is not even directed to synthesis of reboxetine enantiomers; rather, the reference is directed to an HPLC-based method for

the determination of the type and amount of reboxetine enantiomers in a sample. Synthesis of reboxetine enantiomers is only briefly mentioned in the "Introduction" section of the Frigerio *et al.* reference. In fact, the reboxetine enantiomers discussed in the reference were obtained from the "Chemical Development Department of Farmitalia Carlo Erba" and were not synthesized by the authors of the Frigerio *et al.* reference (see page 352, column 2, first sentence of "Chemicals and solutions" section of the Frigerio *et al.* reference). Thus, the Frigerio *et al.* reference does not teach or suggest anything regarding racemization of a single enantiomer of methylphenidate to produce all four possible enantiomers.

The remaining supplementary references, the Yakhotov and Kratchanov references, are cited by the Examiner as evidence that all four enantiomers of methylphenidate can exist together. Appellants do not deny that all four enantiomers of methylphenidate can exist together. However, the fact that all four enantiomers of methylphenidate can exist together is irrelevant to Appellants' claimed invention and the issue of whether prior art taught a means to racemize a single enantiomer of methylphenidate into all four enantiomers. Appellants' point is simple: the references cited by the Examiner, taken alone or in combination, do not teach or suggest a means for taking a single enantiomer of methylphenidate and racemizing it so as to produce all four enantiomers of methylphenidate.

In response to Appellants' arguments submitted during prosecution of the '139 application regarding the failure of the cited references to teach or suggest a means for racemizing a molecule, such as methylphenidate, having two chiral centers within one molecule so as to produce all four possible stereoisomers from a single enantiomer of the molecule, the Examiner stated in the Office Action dated December 19, 2003 that

> Applicant's argument is based on racemization of the "two chiral" center. Please note that **racemization involving two chiral center was disclosed by Miller** see col. 2 **R,S-HPCA.DAA etc. which are material with two chiral center** which are racemized for additional S-enantiomer (see col. 1 line 65-66). Criticality in racemization into "four" enantiomers, thus, is not because of the "two" chiral centers but the conditions employed to ensure all four enantiomers are formed simultaneously. Just because the prior art such as Rometsch did not *name* all four enantiomers, does not mean the racemization using the same acid would not give all four enantiomers. Such can only be obviated by *factual* comparison. (emphasis added)

As an initial matter, Appellants assert that the '261 Miller patent, which the Examiner appears to be referencing in the remarks quoted above, does not teach or suggest methods for racemization of HPCA. Nowhere in the '261 Miller patent is racemization of an enantiomer of HPCA into a mixture of R-HPCA and S-HPCA taught; all of the disclosure in the '261 Miller patent is directed to starting with a racemic mixture, *i.e.*, R,S-HPCA, and resolving the racemate to produce a single enantiomer of HPCA. Resolution of a racemic mixture to obtain an enantiomer is the opposite of racemization of an enantiomer to obtain a racemic mixture. The only mention of racemization in the '261 Miller patent is at column 1, lines 64-66, where it is indicated that the R-enantiomer of HPCA can be used to produce the S-enantiomer of HPCA upon racemization; however, the disclosure of the '261 Miller patent does not teach how to racemize the R-enantiomer (or the S-enantiomer) to produce a racemic mixture of HPCA. The Miller abstract, as noted in the preceding paragraph, does disclose racemizing an enantiomer of HPCA; however, as is also noted in the preceding paragraph, there is no teaching or suggestion in the Miller abstract of racemizing an enantiomer of a molecule that has two chiral centers. In addition, the Miller abstract does not teach or suggest racemization by reacting an unwanted enantiomer with an acid, as is recited in Appellants' claims.

If one assumes from the Examiner's statement in the December 19, 2003 Office Action ". . . R,S-HPCA.DAA etc. which are [sic] material with two chiral center . . ." that the Examiner is asserting that "R,S-HPCA.DAA" described in the '261 Miller patent is a single molecule having two chiral centers, then Appellants respectfully disagree. The "R,S-HPCA.DAA" that the Examiner refers to in the '261 Miller patent is **not** a single molecule, but rather is a **salt** composition formed of one molecule of the organic compound HPCA and one molecule of the organic compound DAA. The individual chemical structure of HPCA is shown at column 1, lines 50-58, of the '261 Miller patent and the individual chemical structure of DAA is shown at column 2, lines 1-10, of the '261 Miller patent. Thus, two distinct molecules make up the R,S-HPCA.DAA salt composition. Appellants note that reference is made throughout the '261 Miller patent to the "R,S-HPCA.DAA salt" and that the salts can be converted to the HPCA free acid. Moreover, as noted previously, HPCA has only one chiral center and DAA may have only one chiral center. Furthermore, as

Appellants have noted previously, the '261 Miller patent only discloses a racemate of the HPCA molecule itself; the DAA molecule does not undergo racemization.

Appellants respectfully assert that any assumption by the Examiner that the use of methods described in any of the cited references will result in racemization at both chiral centers of methylphenidate is incorrect. Appellants respectfully assert that one need look no farther than the Rometsch patent (U.S. Patent No. 2,957,880) cited in the Office Action dated December 19, 2003 as evidence that the prior art does not teach or suggest means to racemize methylphenidate at both of its chiral centers. Consideration of the molecular structure of methylphenidate would suggest to the ordinarily skilled artisan that one of the two chiral centers of the molecule can be racemized much more easily than the other, thereby leading to the production of fewer than all four possible stereoisomers. This is clearly supported by the experimental results disclosed in the Rometsch patent. Example 6 of the Rometsch patent discloses epimerisation of methylphenidate with base; however, only one of the two chiral centers of the methylphenidate molecule is racemized, which thereby results in a mixture of diastereomers (*i.e.*, fewer than all of the four possible stereoisomers of methylphenidate are produced). The results disclosed in the Rometsch patent teach that when one started with a single enantiomer of methylphenidate and attempted racemization thereof, both chiral centers of methylphenidate were not racemized.

Using the nomenclature of the Rometsch patent, the racemizations described at column 2, lines 19-27, of the patent are:

1) $a_1 + a_2 \rightarrow a_1 + a_2 + b_1 + b_2$,

2) $a_1 \rightarrow a_1 + b_1$

and

3) $a_2 \rightarrow a_2 + b_2$,

wherein

a_1 = *d-erythro*-methylphenidate

a_2 = *l-erythro*-methylphenidate

b_1 = *d-threo*-methylphenidate

b_2 = *l-threo*-methylphenidate.

In reaction (1), the starting materials include two different enantiomers (a_1 and a_2) of methylphenidate and, therefore, racemization is not proceeding from a single enantiomer starting material. In reactions (2) and (3), only two of the four possible enantiomers result from each reaction. It is clear from the Rometsch patent disclosure that these conversions involve "scrambling" at only one (not both) chiral center of the methylphenidate molecule. Column 2, lines 25-27, of the Rometsch patent confirms this, wherein it is stated that "... **contrary to expectation** the rearrangement in this process takes place at **only one of the two** asymmetrical carbon atoms." (emphasis added). Thus, it is explicitly acknowledged in the Rometsch patent disclosure that racemization of a single enantiomer of methylphenidate did not result in racemization at both of the chiral centers of the molecule and, therefore, did not produce all four possible stereoisomers from a single enantiomer of methylphenidate. Accordingly, Appellants respectfully assert that the cited Rometsch patent teaches away from Appellants' claimed invention in that the Rometsch patent specifically discloses that racemization of methylphenidate occurs at only one of the two chiral centers of the molecule and, therefore, Appellants' surprising ability to racemize methylphenidate at both chiral centers to thereby produce all four stereoisomers from a single enantiomer of methylphenidate is not taught or suggested.

Appellants also note that dependent claim 8 specifies that the racemization step of claim 1 comprises the use of a carboxylic acid and dependent claim 3 specifies that an achiral carboxylic acid is utilized. Appellants respectfully assert that the references cited under the §103 rejections do not teach or suggest complete racemization of a single enantiomer of methylphenidate (or a molecule that has two chiral centers and is structurally analogous to methylphenidate) using a carboxylic acid as in claim 8 or an achiral carboxylic acid as in claim 3. In the absence of a teaching or suggestion in the art, and a reasonable expectation of success, to effect complete racemization of the molecule using the claimed acid, a *prima facie* case of obviousness is not established for the claims.

Appellants further note that in regard to the Harris patent (U.S. Patent No. 6,242,464), Appellants respectfully assert that the Harris patent is disqualified under 35 USC §103(c). The issue of disqualification of the Harris patent under 35 USC §103(c) is discussed in detail in section VIII, subsection D, of this Supplemental Appeal Brief. However, for purposes of addressing this reference under this rejection, Appellants respectfully note that Appellants' undersigned representative

previously stated in a clear and conspicuous manner in the Amendment dated August 14, 2003, that "at the time the invention of the subject application was made, the subject application and U.S. Patent No. 6,242,464 were commonly owned by, or subject to an obligation of assignment to, Chiroscience Limited." The Examiner did not provide an explanation as to why the statement was not accepted and did not provide the required explanation as to why the accuracy of the statement was doubted. Accordingly, Appellants respectfully assert that the statement submitted in the August 14, 2003 Amendment is sufficient to disqualify the Harris patent from being used in a rejection under 35 USC 103(a) against the subject '139 application.

Also attached as Appendix C of this Appeal Brief is a Declaration of Dr. Hooshang S. Zavareh Under 37 CFR 1.132. Appellants also note that Dr. Zavareh's Declaration was submitted with the Amendment dated August 14, 2003 and, therefore, is already of record in the '139 application. In his Declaration, Dr. Zavareh points out that racemization of an enantiomer of methylphenidate so that all four enantiomers are obtained requires abstraction of a proton. Dr. Zavareh states that it is, therefore, surprising that an acid, as is recited in the claimed method, could be used to racemize a single enantiomer of methylphenidate into all four possible enantiomers. The Examiner has not provided any arguments or evidence to rebut or question the statements or conclusions in Dr. Zavareh's Declaration.

In addition, Appellants have also attached as Appendix D of this Appeal Brief an article by Dr. Mahavir Prashad entitled "Approaches to the Preparation of Enantiomerically Pure (*2R,2'R*)-(+)-*threo*-Methylphenidate Hydrochloride" (2001, *Adv. Synth. Catal.*, Vol. 343, No. 5, pp. 379-392). Appellants note that this article was published after the effective filing date of the '139 application. Appellants also note that this article was submitted with the Amendment dated August 14, 2003 and, therefore, is already of record in the '139 application. The article indicates that the author, Dr. Prashad, is a senior fellow and group leader in the Process R&D section of Chemical and Analytical Development at the Novartis Institute for Biomedical Research. The article is a review article and concerns methods for producing enantiomerically pure methylphenidate. A portion of Dr. Prashad's article (from page 383, section 4) is reprinted below:

> A resolution process is more attractive and economical if the undesired enantiomer can be recycled via racemization. However, in the case of methylphenidate, such a

> **racemization is challenging** because there are two stereogenic centers which have to be epimerized. A method to affect the racemization at both stereogenic centers has been demonstrated by refluxing a solution of *(2R,2'R)-threo*-methylphenidate (1) with propionic acid in toluene to afford a mixture of four stereoisomers in roughly equal proportions. (citing published International Application No. WO 97/28124) (emphasis added)

First, Dr. Prashad indicates that "racemization [of methylphenidate] is challenging" because there are two chiral centers in the molecule. This is precisely the point that Appellants have argued during prosecution of the '139 application and that the Examiner has repeatedly failed to address or appreciate: racemization of a molecule of methylphenidate having two chiral centers so as to produce all four possible stereoisomers is not conventional or obvious. It is the presence of two chiral centers in one molecule that makes complete racemization starting from a single enantiomer "challenging."

Second, Dr. Prashad also references published International Application WO 97/28124 as the first publication to describe a successful means for the complete racemization of a single enantiomer of methylphenidate into all four stereoisomers. Dr. Prashad does not reference any other publications as teaching or suggesting a means for racemization of single enantiomer methylphenidate into all four possible enantiomers. Published application WO 97/28124 application, a copy of which is attached with this Appeal Brief as Appendix E, is the corresponding international filing of the subject '139 application. Appellants chose to file an international PCT application (international application No. PCT/GB97/00281, which was published as WO 97/28124) and a separate U.S. utility application (*i.e.*, application Serial No. 08/792,415 filed February 3, 1997, which is the parent application to the subject '139 application) under 35 USC §111 (rather than designating the U.S. in the international application and subsequently filing a national stage application under 35 USC §371). Appellants note that the subject '139 application and the WO 97/28124 application have identical inventorship, claim priority to the same British patent applications, and have the same disclosure in the specification. Thus, Dr. Prashad is, in essence, referencing the subject '139 application as teaching the first successful means for the complete racemization of a single enantiomer of methylphenidate into all four stereoisomers. The Examiner has not provided any arguments or evidence to rebut or address the statements by Dr. Prashad.

Accordingly, Dr. Zavareh's Declaration Under 37 CFR 1.132 and the published article by Dr. Prashad provide further evidence as to the nonobviousness of claims 1-8 of the '139 application.

The subject '139 application teaches how to racemize a single enantiomer of methylphenidate to produce all four individual enantiomers; this was both novel and nonobvious. The references cited by the Examiner do not teach or suggest how to racemize a single enantiomer of methylphenidate, or any other single molecule structurally analogous to methylphenidate and having two chiral centers, to produce all four individual enantiomers. In view of the above arguments and evidence presented herein, Appellants respectfully request reversal of all of the rejections set forth under 35 USC §103(a).

C. Claims 1-8 are not *prima facie* obvious over claim 1 of U.S. Patent No. 6,121,453 (Zavareh) in view of Miller (abstract (1980)), Barry (1993) or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

1. Statement of the rejection based on "obviousness-type" double patenting.

Claims 1-8 are unpatentable under the judicially created doctrine of obviousness-type double patenting over claim 1 of U.S. Patent No. 6,121,453 (Zavareh) in view of Miller (abstract (1980)), Barry (1993) or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464).

The basis for the rejection of U.S. Patent No. 6,121,453 (hereinafter referred to as the Zavareh patent) in view of Miller (abstract (1980)), Barry (1993) or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464), as set forth in the Office Action dated September 29, 2004, is quoted below:

> *Determination of the scope and content of the prior art (MPEP §2141.01)*
> Zavarch [sic] claimed a processe [sic] for making a single enantiomer of d-threo-methylphenidate or l-threo-methylphenidate from racemic mixtures. See claim 1.
>
> *Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)*
> Zavarch [sic] claimed a similar process with all the claimed elements **except** wherein a recycle by racemization step was not included. Barry taught that in preparation of amino acid esters (please note that the instant methylphenidate is a

cyclic amino acid ester) analogous to the claims, racemization is achieved under acidic conditions and the analogous art by Miller (CA 94) or '261 taught that recycling the racemized isomers would give more of the intended isomer (see Miller abstract and '261 col. 1 lines 64-66). In addition, both heat and acid were taught by the prior art as agents for racemization (see Barry and Miller).

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references placed the single enantiomer, process of making and alternative choices for increasing yield of a single isomeric form in the possession of an artisan in the field. It would have been prima facie obvious to employ a conventional modification of recycle/racemization step for the issued co-owned claim 1 of Zavarch [sic] **because** addition of a recycle/racemization step to produce higher yields of a desirable single isomer is expected, and such expectation is the attributes taught by the prior art. In the absence of unexpected results, the instant claims are an unreasonable prolonging of exclusive rights by the addition of prima facie obvious steps to the process.

2. A *prima facie* case of obviousness has not been established against claims 1-8.

Appellants respectfully assert that the claimed invention is not obvious over the cited references, regardless of whether the references are taken alone or in combination. In order to establish a *prima facie* case of obviousness, the prior art must teach or suggest each and every element and limitation of the claimed invention, and provide a reasonable expectation of success that the modification or combination will succeed. *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988). A *prima facie* case of obviousness has not been established against claims 1-8 in the subject '139 application because none of the cited references, either alone or in the combination asserted by the Examiner, teach or suggest each and every element of Appellants' claimed invention, nor do they provide the required reasonable expectation of success.

The Examiner asserts under this rejection that claim 1 of the Zavareh patent teaches all of the elements of Appellants' claimed invention "except wherein a recycle by racemization step was not included." Appellants respectfully disagree. Claim 1 of the Zavareh patent reads "A process for preparing substantially single enantiomer d-threo-methylphenidate, which proceeds by means of a classical salt resolution using (-)-menthoxyacetic acid." In contrast, claim 1 of the '139 application recites elements that are not recited in claim 1 of the Zavareh patent, including, for example, "...enriching said mixture following racemisation wherein the *d-threo* and *l-threo* stereoisomers of

methylphenidate are enriched over the *d-erythro* and *l-erythro* stereoisomers of methylphenidate;..." Claim 1 of the Zavareh patent does not teach enriching a mixture of all four stereoisomers of methylphenidate following a racemization step, nor do any of the secondary references cited under this rejection.

Claim 4 of the '139 application, which is included under this rejection, recites that separation of the *d-erythro* and *l-erythro* stereoisomers in the claimed method is conducted following hydrolysis of the mixture of stereoisomers, to give ritalinic acid, and before or after re-esterification of the acid. Claim 5 of the '139 application, which is also included under this rejection, recites that the method of claim 4 additionally comprises equilibrating the product of hydrolysis such that the *threo* diastereomer is preferentially obtained. Claim 1 of the Zavareh patent does not teach the elements of either of these claims, nor do any of the secondary references cited under this rejection.

Claim 7 of the '139 application, which is included under this rejection, recites the use of *O,O'*-ditoluoyltartaric acid in the resolution step of the claimed method. Claim 1 of the Zavareh patent does not teach resolution using O,O'-ditoluoyltartaric acid, nor do any of the secondary references cited under this rejection.

Thus, Appellants respectfully assert that claim 1 of the Zavareh patent does not teach or suggest all of the elements of Appellants' claimed invention "except wherein a recycle by racemization step was not included."

In regard to the secondary references cited under the obviousness-type double patenting rejection, Appellants respectfully reassert their comments presented herein addressing the same secondary references cited in the rejections under 35 USC §103(a) and hereby incorporate those remarks by reference in their entirety. As noted in regard to the rejections under 35 USC §103(a), none of the secondary references teach or suggest means for racemization of a single enantiomer of methylphenidate, or any other single molecule analogous in structure to methylphenidate and having two chiral centers, so as to produce all four individual enantiomers. As also noted previously, the Barry reference only discloses amino acid esters (*e.g.*, leucine methyl ester) that have only one chiral center within the molecule itself. Thus, any racemization that may be taught in the Barry reference is racemization of a molecule with a single chiral center, and not racemization of a single molecule with two chiral centers as provided in Appellants' claimed invention. Therefore, the amino acid

esters taught in the Barry reference are not structurally analogous to methylphenidate and the racemization of such amino acid esters is not analogous to the racemization of methylphenidate.

In view of the arguments and remarks presented herein, Appellants respectfully request reversal of the rejection of claims 1-8 as unpatentable for obviousness-type double patenting over claim 1 of U.S. Patent No. 6,121,453 (Zavareh) in view of Miller (abstract (1980)), Barry (1993) or Miller (U.S. Patent No. 4,254,261) further in view of Harris (U.S. Patent No. 6,242,464)

D. The Harris patent (U.S. Patent No. 6,242,464) is disqualified as prior art under 35 USC §103(c) in the rejection under 35 USC §103(a) in which the Harris patent is cited.

As an initial matter, Appellants note that this issue regarding disqualification of the Harris patent was argued by Appellants in the Appeal Brief dated July 19, 2004. However, in the subsequent Office Action dated September 29, 2004, the Examiner did not acknowledge or address Appellants assertions regarding the disqualification of the Harris patent.

Appellants note the subject '139 application was filed August 10, 2001 but is entitled under 35 USC §120 to the benefit of the filing date of U.S. parent application Serial No. 08/792,414, filed February 3, 1997, which claims priority under 35 USC §119(e) to U.S. provisional application Serial No. 60/021,135, filed September 12, 1996. Because the '139 application was filed after November 29, 1999, it is entitled to the provisions of 35 USC §103(c). The Harris patent (U.S. Patent No. 6,242,464) was filed January 22, 1997 and claims priority to a provisional application filed March 21, 1996. Thus, U.S. Patent No. 6,242,464 only qualifies as prior art against the subject '139 application under 35 USC §102(e). Appellants' undersigned representative previously stated in a clear and conspicuous manner in the Amendment dated August 14, 2003, that "at the time the invention of the subject application was made, the subject application and U.S. Patent No. 6,242,464 were commonly owned by, or subject to an obligation of assignment to, Chiroscience Limited." In the Office Action dated December 19, 2003, the Examiner (apparently in response to Appellants' statement regarding common ownership submitted in the August 14, 2003 Amendment) stated that "the record of [the '139] application is not clear as to "common" ownership as described in the response. Submission of record is required." Appellants respectfully assert that the statement submitted in the August 14, 2003 Amendment is sufficient to disqualify U.S. Patent No. 6,242,464

from being used in a rejection under 35 USC 103(a) against the subject '139 application. In regard to the evidence required to establish common ownership, section 706.02(l)(2), part II, of the MPEP instructs examiners that

> The following statement is sufficient evidence to establish common ownership of, or an obligation for assignment to, the same person(s) or organization(s):
>
> > *Applications and references (whether patents, patent applications, patent application publications, etc.) will be considered by the examiner to be owned by, or subject to an obligation of assignment to the same person, at the time the invention was made, if the applicant(s) or an attorney or agent of record makes a statement to the effect that the application and the reference were, at the time the invention was made, owned by, or subject to an obligation of assignment to, the same person.*
>
> See "Guidelines Setting Forth a Modified Policy Concerning the Evidence of Common Ownership, or an Obligation of Assignment to the Same Person, as Required by 35 U.S.C. 103(c)," 1241 O.G. 96 (December 26, 2000). **The applicant(s) or the representative(s) of record have the best knowledge of the ownership of their application(s) and reference(s), and <u>their statement of such is sufficient evidence</u>** because of their paramount obligation of candor and good faith to the USPTO.
>
> ... Applicants may, **but are not required to**, submit further evidence, such as assignment records, affidavits or declarations by the common owner, or court decisions, *in addition to* the above-mentioned statement concerning common ownership. (emphasis added)

Thus, the Patent Office's own rules and instructions clearly indicate that further evidence beyond the statement by Appellants' undersigned representative regarding common ownership of the subject '139 application and U.S. Patent No. 6,242,464 in the Amendment dated August 14, 2003 is <u>not</u> required and, in the absence of an explanation by the Examiner of a reason to doubt the accuracy of the statement, should have been accepted by the Patent Office. In regard to an examiner's reason to doubt the accuracy of a statement, MPEP section 706.02(l)(2), part II, states

> **In rare instances, the examiner may have independent evidence that raises a material doubt as to the accuracy of applicant's representation** of either (1) the

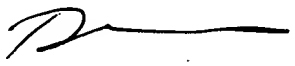
> common ownership of, or (2) the existence of an obligation to commonly assign, the application being examined and the applied U.S. patent or U.S. patent application publication reference. **In such cases, the examiner may explain why the accuracy of the representation is doubted**, and require objective evidence of common ownership of, or the existence of an obligation to assign, the application being examined and the applied reference as of the date of invention of the application being examined. (emphasis added)

The Examiner in the subject '139 application has not indicated that independent evidence exists that raises a material doubt as to the accuracy of the statement by Appellants' representative, nor has the Examiner offered an explanation why the accuracy of the statement by Appellants' undersigned representative is in doubt. Therefore, Appellants respectfully assert that the Examiner's refusal to accept the statement regarding common ownership of the subject '139 application and Patent No. 6,242,464 is not in compliance with MPEP 706.02(l)(2) part II. Accordingly, in the absence of an appropriate explanation for not accepting the statement regarding common ownership by Appellants' undersigned representative, Appellants respectfully assert that the statement in the Amendment dated August 14, 2003 should be accepted by the Patent Office.

The subject '139 application is a continuation application of U.S. application Serial No. 08/792,415. The inventors assigned their rights in the 08/792,415 application in February of 1997 to Chiroscience Limited. The assignment to Chiroscience Limited in the 08/792,415 application was recorded in the Patent Office on May 1, 1997, at reel/frame: 8483/0885. U.S. Patent No. 6,242,464 (the Harris patent) was owned by Chiroscience Limited at the time the subject invention was made. Chiroscience Limited is listed as the assignee on the front cover of U.S. Patent No. 6,242,464 and the assignment to Chiroscience Limited was recorded in the Patent Office on April 28, 1997, at reel/frame 8477/0821. Appellants' undersigned representative hereby states again that, at the time the invention of the subject '139 application was made, the subject application and U.S. Patent No. 6,242,464 were commonly owned by, or subject to an obligation of assignment to, the same entity: Chiroscience Limited. Accordingly, under 35 USC §103(c), the subject matter of the Harris patent cannot be used in a rejection of the claimed invention under 35 USC §103(a). Reversal of the rejection under 35 USC §103(a) that relies on the Harris patent as a secondary reference is respectfully requested in view of the disqualification of the Harris patent.

In view of the foregoing, Appellants urge that the Board reverse the 35 USC §103(a) obviousness rejections and the obviousness type double patenting rejection of record in the subject '139 application and that this application be passed to issuance.

Respectfully submitted,



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Attachments:
Appendix A: Currently Pending Claims
Appendix B: Copy of Frigerio *et al.* (1994) reference
Appendix C: Declaration of Dr. Hooshang S. Zavareh Under 37 CFR 1.132 dated July 15, 2003
Appendix D: Copy of published article by Mahavir Prashad (2001)
Appendix E Copy of Published International Application WO 97/28124